1. Record Nr. TD17008767

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Titolo	Cell death mechanisms triggered by monoclonal antibodies against CD99 in Ewing sarcoma: Cross-talk between MDM2, IGF-1R and Ras/MAPK [Tesi di dottorato]
Lingua di pubblicazione	Non definito
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	In relazione con http://amsdottorato.unibo.it/6560/
Sommario	CD99 is a 32 kDa transmembrane protein whose high expression characterizes Ewing sarcoma (ES), a very aggressive pediatric bone tumor. In addition to its diagnostic value, CD99 has therapeutic potential since it leads to rapid and massive ES cell death when engaged with specific antibodies. Here a novel mechanism of cell death triggered via CD99 is shown, leading, ultimately, to the appearance of macropinocytotic vescicles. Anti-CD99 mAb 0662 induces MDM2 ubiquitination and degradation, which causes not only a p53 reactivation but also the IGF-1R induction and its subsequent internalization; CD99 results internalized together with IGF-1R inside endosomes, but then the two molecules display a different sorting: CD99 is degraded, while IGF-1R is recycled on the surface, causing, as a final step, the up-regulation of RAS-MAPK. High-expressing CD99 mesenchymal stem cells show mild Ras induction but no p53 activation and escape cell death, but in presence of EWS/FLI1 mesenchymal stem cells expressing CD99 show a stronger Ras induction and a p53 reactivation, leading to a significant cell death rate. We propose that CD99 triggering in a EWS/FLI1-driven oncogenetic context creates a synergy between RAS upregulation and p53 activation in ES cells, leading to cell death. Moreover, our data rule out possible concerns on toxicity related to the broad CD99 expression in normal tissues and provide the rationale for the

	therapeutic use of anti-CD99 MAbs in the clinic.
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